Population Pharmacokinetics and Pharmacodynamics Modeling To Optimize Dosage Regimens of Sulbactam in Critically Ill Patients with Severe Sepsis Caused by *Acinetobacter baumannii*

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Sulbactam is being considered as an alternative concomitant medication with other effective antibiotics for the treatment of multidrug-resistant (MDR) *Acinetobacter baumannii* infections. Pathophysiological changes in critically ill patients with severe sepsis, resulting in altered pharmacokinetic (PK) patterns for antibiotics, are important factors in determining therapeutic success. The aims of this study were (i) to examine the population PK parameters and (ii) to assess the probability of target attainment (PTA) for sulbactam in patients with severe sepsis caused by *A. baumannii*. PK studies were carried out following administration of 2 g of sulbactam every 12 h on the 4th day of drug administration in 27 patients, and a Monte Carlo simulation was performed to determine the PTA of achieving 40% exposure time during which the plasma drug concentration remained above the MIC ($T_{>MIC}$) and 60% $T_{>MIC}$. The central and peripheral volumes of distribution were 14.56 and 9.55 liters, respectively, and total clearances of sulbactam were 2.26 liters/h and 7.64 liters/h in patients aged >65 years and ≤65 years, respectively. The high PTAs (≥90%) for targets of 40% $T_{>MIC}$ and 60% $T_{>MIC}$ with a MIC of 4 μg/ml were observed when sulbactam was administered by a 4-h infusion of 1 g every 12 h and 1 g every 8 h, respectively. Sulbactam would be an alternative antibiotic option to coadminister with colistin for the treatment of infections caused by MDR *A. baumannii*. However, for pathogens with MICs of >4 μg/ml, higher dosage regimens of sulbactam are required.

The emergence of multidrug-resistant (MDR) microorganisms worldwide has become a significant public health threat and remains a cause of increased rates of morbidity and mortality in critically ill patients with severe sepsis (1, 2). *Acinetobacter* species, especially *Acinetobacter baumannii*, have been shown to be associated with serious nosocomial infections in critically ill patients in intensive care units for several years. These microorganisms have developed resistance to several classes of antimicrobial agents, resulting in the dangerous situation of physicians having only a few, or even sometimes no, effective antibiotics for the treatment of infections caused by MDR *A. baumannii* (3, 4). Sulbactam, a β-lactamase inhibitor, has a major role in irreversible binding to block the activity of β-lactamase produced by bacteria against β-lactam antibiotics, and in particular, this agent has intrinsic activity against *Acinetobacter* spp. (5, 6). Therefore, this agent is being considered as an alternative concomitant medication with other effective antibiotics for the treatment of these pathogens.

Sulbactam exhibits primarily time-dependent killing, and the percentage of the exposure time during which the free drug concentration remains above the MIC (% $T_{>MIC}$) is the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with efficacy (7). This agent has been shown to be 93% stable for 24 h at 37°C (8). Therefore, a continuous or prolonged infusion would be the appropriate mode of administration of sulbactam to maximize this parameter. Pathophysiological changes in critically ill patients with severe sepsis resulting in altered PK patterns, including volume of distribution (*V*) and total clearance (CL), have been found with several antimicrobial agents that may affect therapeutic plasma concentrations and the achievement of PD targets for antimicrobial therapy (9, 10). However, to date, there have been limited PD studies (11) and the optimal dosage regimens of sulbactam for the treatment of *Acinetobacter* species infections in this patient population are still unknown. The aims of the study were (i) to determine a population PK model to describe the disposition of sulbactam and (ii) to assess the efficacy of various dosage regimens of sulbactam in terms of probability of target attainment (PTA) over a range of MICs in critically ill patients with severe sepsis caused by MDR *A. baumannii*.

MATERIALS AND METHODS

Subjects. The study was conducted with 27 patients with severe sepsis admitted to Songklanagarind Hospital, the largest tertiary care center in southern Thailand, between September 2014 and December 2015. Patients who met the following criteria were eligible for the study: (i) >18 years of age and (ii) having a diagnosis of severe sepsis (12) caused by MDR *A. baumannii*. Bacteremia was defined by at least one positive hemoculture. Hospital-acquired pneumonia was diagnosed as an infection which developed in a patient who had been hospitalized for ≥48 h. Ventilator-associated pneumonia (VAP) was diagnosed as an infection which

developed in a patient who had been intubated and receiving mechanical ventilation for ≥48 h in the hospital. Catheter-associated urinary tract infection was defined by a urine culture with ≥10⁵ colony counts/ml in a hospitalized patient with an indwelling urethral catheter. Patients who were pregnant, had documented hypersensitivity to sulbactam, or had a history of chronic kidney disease were excluded from the study. The severity of illness for each patient was assessed at the time of enrollment into the study, using the acute physiology and chronic health evaluation II (APACHE II). The protocol for the study was approved by the ethics committee of Songklanagarind Hospital. Written informed consent was obtained from each subject or a legally acceptable representative before enrollment.

Drugs and chemicals. Sulbactam (Sibatam) was donated by the Siam Pharmaceutical Co., Ltd. (Bangkok, Thailand). Sulbactam standard powder and ofloxacin (internal standard) were purchased from U.S. Pharmacopeial Convention (Rockville, MD, USA) as pure powder. All solvents were of high-performance liquid chromatography (HPLC) grade.

Study design. All patients received a 1-h infusion of 2 g of sulbactam diluted in 100 ml of normal saline solution, delivered via infusion pump at a constant flow rate, every 12 h, coadministered with colistin for 10 days. Sulbactam PK studies were carried out on the 4th day (the 7th dose) of drug administration, and a Monte Carlo simulation (MCS) was performed to assess the efficacy of sulbactam for 1-h and 4-h infusions of 1 g every 12 h, 1 g every 8 h, 1 g every 6 h, 2 g every 12 h, 2 g every 8 h, 2 g every 6 h, 3 g every 8 h, 3 g every 6 h, and 4 g every 8 h and for 3-, 6-, 9-, and 12-g doses administered every 24 h as a continuous infusion. Each patient received sulbactam at room temperature (32 to 37°C).

Blood sampling. Sulbactam PK studies were carried out on the 4th day of sulbactam administration (0 to 12 h after the start of the 7th dose of sulbactam administration). Blood samples (~3 ml) were obtained by direct venipuncture at the following times: shortly before (time zero) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 h after the start of sulbactam administration. All blood samples were added to a heparinized tube and centrifuged at 1,000 × g for 10 min at 4°C within 5 min. All plasma samples were stored at −80°C until analysis within 1 week.

Sulbactam assay. Blood concentrations of sulbactam were determined by reverse-phase HPLC. The samples were prepared by the modified method described by Abu-Shandi (13). Briefly, 200 μl of 2 M imidazole was added to 500 μl of plasma sample, which was vortexed for 10 s, and then the mixture was kept at 60°C for 50 min to allow complete derivatization and finally cooled at room temperature for 15 min. A 100-μl volume of a 313-μg/ml concentration of ofloxacin, as an internal standard, was added to the mixture sample, which was then vortexed for 5 s. The internal standard sample was treated with 700 μl of acetonitrile for protein precipitation, vortexed for 30 s, and centrifuged at 17,800 × g for 30 min at 4°C. A 20-μl aliquot of the sample was injected onto a Capcell Pak C₁₈ column (150 mm by 4.6 mm inside diameter, 5-μm particle size; Shiseido Co., Ltd., Tokyo, Japan) placed in a Shimadzu CTO-20A column oven (Shimadzu Corporation, Tokyo, Japan) set at 50°C using a Shimadzu LC-20AD quaternary pump (Shimadzu Corporation, Tokyo, Japan) and a Shimadzu SIL-20A thermostat autosampler (Shimadzu Corporation, Tokyo, Japan) at 4°C. The mobile phase was an isocratic phase of acetonitrile and phosphate buffer (22:78, vol/vol) at a flow rate of 1.5 ml/min. The phosphate buffer consisted of 5 mM tetrabutyl-ammonium bromide, 1 mM disodium hydrogen phosphate, and 1 mM sodium dihydrogen phosphate. The column effluent was monitored at 320 nm with a Shimadzu SPD-M20A diode array detector (Shimadzu Corporation, Tokyo, Japan). Peaks were recorded and integrated with an LCsolution version 1.22SP1 (Shimadzu Corporation, Tokyo, Japan). The lower limit of quantification was 0.5 μg/ml. The intra-assay reproducibility values, characterized by coefficients of variation (CVs), were 2.74%, 2.02%, and 2.40% for samples containing 1.5, 25, and 45 μg/ml, respectively. The interassay reproducibility precision values, calculated as CVs, were 2.12%, 1.30%, and 2.56% for samples containing 1.5, 25, and 45 μg/ml, respectively.

Pharmacokinetic analysis. The plasma sulbactam concentration versus time data were analyzed by nonlinear mixed-effect modeling using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD, USA). The NONMEM runs were executed by PDx-Pop version 5.2 (ICON Development Solutions, Ellicott City, MD, USA). The data were fitted to one-, two-, and three-compartment models using subroutines from the NONMEM library (14). First-order conditional estimation with interaction (FOCEI) and stochastic approximation expectation maximization (SAEM) methods were examined to estimate the PK parameters. An exponential model was used to describe intersubject variability, and a combined (additive and proportional) error model was used to describe residual variability. After the base model was obtained, the relationships between the PK parameters and clinical covariates were explored by visual inspection of scatter and box plots (continuous and categorical variables, respectively). The following covariates were evaluated: actual body weight (kg), ideal body weight (kg), age (years), gender, creatinine clearance (CL$_{CR}$) estimated by the Cockroft and Gault equation (ml/min), CL$_{CR}$ estimated by the Modification of Diet in Renal Disease equation (ml/min), hemoglobin (g/dl), hematocrit (%), and Glasgow Coma Scale (GCS) and APACHE II scores. If a trend between a covariate and a PK parameter was found, then the covariate was considered for inclusion in the base model. Covariates were kept in the model if there were significant improvements in the fit over the base model. Based on a χ^2 test in stepwise approach, a decrease in the minimum objective function value (MOFV) of 3.84 U was considered significant ($P < 0.05$) in the forward addition step and an increase in the MOFV of 6.61 U was considered significant ($P < 0.01$) in the backward deletion step. Continuous covariates were scaled to their median values.

A statistical comparison of models was based on differences in MOFV. Goodness-of-fit of models were evaluated by visual inspection of the diagnostic scatter plots, including observed and predicted concentrations versus time, weighted residual error versus time, and weighted residual error versus predicted concentrations. One thousand bootstrap runs were performed to assess the robustness of all pharmacokinetic parameter estimates in the final model. In addition, a visual predictive check was performed by simulating 1,000 subjects to assess the predictive performance of the final model. The visual checks and representative percentiles (5th, 10th, 50th, 90th, and 95th percentiles) were visually assessed.

Pharmacodynamic assessment using Monte Carlo simulation. The covariates between the PK parameters were used in the MCS. The Choleski decomposition matrix of the covariate between all PK parameters was multiplied with a simulated standardized Z-score before being rescaled to mimic the actual PK parameters. Simulation of the PK parameters was performed in log-normal scale (15) and was validated to confirm that they could retain their statistical properties (mean, standard deviation, correlation matrix) of the original parameters. The simulated PK parameters were used for solving the two-compartment model equations with a Runge-Kutta order 4 algorithm for each dosage regimen to achieve the concentration-time profiles (16). Hence, $T_{>MIC}$ could be computed from each simulation. The simulation program was written in the Basic language, using a validated subroutine and compiled with a QuickBasic compiler version 3 of Microsoft Corporation. We simulated 230,000 iterations to calculate the target attainment of each dosage regimen.

RESULTS

Twenty-seven patients were enrolled in the study (17 males and 10 females). Their mean age was 58.30 ± 18.15 years (range, 21 to 81 years), and their mean weight was 59.61 ± 10.90 kg (range, 40 to 83 kg). The characteristics of all patients are shown in Table 1. The current study showed that the MIC$_{50}$ and MIC$_{90}$ of sulbactam against clinically isolated *A. baumannii* isolates were ≤6 μg/ml and ≤32 μg/ml, respectively.

Figure 1 shows the observed concentration-versus-time profile of sulbactam administered by intravenous infusion. A total of 278 plasma concentration samples were analyzed using FOCEI and

TABLE 1 Characteristics of 27 patients with severe sepsis caused by *A. baumannii*[a]

Patient	Body wt (kg)	CL_CR (ml/min) at: Enrollment	CL_CR (ml/min) at: 4th day of study	Source of infection	MIC (μg/ml)	Serum albumin (g/dl)	Fluid balance (liters)	APACHE II score	Concomitant medications	Bacteriological response
1	80.5	102.38	62.48	Bacteremia	1	2.1	+4.30	27	Colistin, imipenem, doxazosin, enoxaparin, metoprolol	Eradicated
2	40	122.78	122.78	VAP	32	1.9	+3.00	29	Colistin, imipenem, vancomycin, enoxaparin, omeprazole, fentanyl, dexamethasone	Eradicated
3	70	89.44	71.37	CAUTI	8	2.2	+4.60	22	Colistin, imipenem, vancomycin, actrapid, omeprazole, midazolam	Eradicated
4	70	59.47	24.02	Septic arthritis	32	1.5	+1.30	12	Colistin, imipenem, omeprazole, fentanyl	Eradicated
5	64	51.93	20.81	HAP	8	3.1	+6.30	15	Colistin, aspirin, cilostazol, simvastatin	Eradicated
6	78.5	272.04	211.10	VAP	4	1.7	+2.90	26	Colistin, enoxaparin, omeprazole	Eradicated
7	50	239.90	77.61	Bacteremia, HAP	6	1.5	+3.20	18	Colistin, imipenem, amiodarone, fentanyl, omeprazole, furosemide	Eradicated
8	83	101.94	44.53	VAP	8	2.1	+2.80	20	Colistin, meropenem, piperacillin-tazobactam, morphine, metoprolol, metronidazole, fentanyl, metoclopramide, nifedipine	Persist
9	53.2	95.33	80.89	VAP	1	2.8	+3.30	22	Colistin, omeprazole, aspirin, morphine	Eradicated
10	65	467.80	381.17	CAUTI	12	1.8	+7.10	13	Colistin, omeprazole, fentanyl	Eradicated
11	60	95.96	83.33	VAP	4	2.2	+2.70	8	Colistin, aminophylline, domperidone, morphine, fentanyl, furosemide	Eradicated
12	60	64.93	33.13	VAP	8	1.8	+14.10	27	Colistin, furosemide, omeprazole, verapamil	Eradicated
13	60	77.96	28.43	Bacteremia	1	1.8	+3.80	29	Colistin, vancomycin, nifedipine, fentanyl	Eradicated
14	61.9	93.01	35.19	Bacteremia	8	1.9	−2.6	22	Colistin, spironolactone, imipenem, omeprazole	Eradicated
15	52	104.95	35.92	HAP	8	2.2	+3.20	16	Colistin, morphine, piperacillin-tazobactam	Eradicated
16	51	48.70	25.00	CAUTI	8	2.2	+6.80	21	Colistin, morphine, omeprazole	Eradicated
17	60	62.38	22.84	VAP	8	2.2	+2.50	20	Colistin, furosemide, metoclopramide, fentanyl	Eradicated
18	48.4	65.76	25.44	VAP	12	1.8	+4.30	29	Colistin, omeprazole, ceftazidime	Eradicated
19	50	56.74	35.25	VAP	48	2.6	−6.90	14	Colistin, imipenem, actrapid, fentanyl, furosemide, insulatard, levophed	Persist
20	52	112.02	121.98	VAP	48	2.8	+3.30	22	Colistin, dormicum, aminophylline	Persist
21	65	111.94	60.19	VAP, CAUTI	4	2.5	+1.00	23	Colistin, imipenem, omeprazole, metoclopramide, fentanyl, furosemide, levophed	Eradicated
22	40	88.29	73.84	VAP	0.75	2.8	+1.70	16	Colistin, omeprazole, fentanyl, simethicone, domperidone, acetylcysteine	Eradicated
23	65	180.56	96.17	VAP	48	1.8	+3.50	12	Colistin, gabapentin, simethicone, omeprazole, metoclopramide	Persist
24	63	201.01	137.73	Bacteremia	0.5	3.1	+6.80	14	Colistin, morphine, dextromethorphan, warfarin, acetylcysteine	Eradicated
25	50	133.29	113.20	VAP	1	3.2	+4.70	18	Colistin, fentanyl	Eradicated
26	57	164.49	148.04	VAP	2	2.9	+2.40	18	Colistin, amlodipine, 50% magnesium sulfate, clexane, paracetamol	Eradicated
27	60	93.28	70.22	VAP	0.75	2.9	+1.80	19	Colistin, meropenem, enalapril	Eradicated

[a] CL_CR, creatinine clearance; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; CAUTI, catheter-associated urinary tract infection; fluid balance, fluid intake minus fluid output for 3 days during the administration of sulbactam; APACHE, acute physiology and chronic health evaluation.

SAEM methods. SAEM was chosen for model building because the estimation step of the SAEM method was more stable while the covariance step of the FOCEI method was difficult to obtain. The two-compartment model significantly reduced the MOFV and the Akaike information criterion (AIC) with acceptable percentages of shrinkage and reasonable parameter estimates. Age as a categorical variable (≤65 years and >65 years) and CL_CR as estimated by the Cockcroft and Gault equation were significant covariates describing the clearance of sulbactam, while hemoglobin was a significant covariate explaining the central volume of distribution, as shown in Fig. 2. The final model was tested with 27 delete-1 data sets. The PK parameter estimates differed from the ones obtained from the original data set by no more than 20%,

suggesting no highly influential data in this analysis. The population pharmacokinetic parameter estimates calculated from the final model are shown in Table 2. The values of the parameters for the base and final models are given in Table 3. All parameter estimates were in the range of the 95% confidence interval (CI) from 1,000 bootstrap runs, indicating the robustness of the final model. Goodness-of-fit plots for the final model (Fig. 3) showed no apparent visual bias for the prediction. A visual predictive check also confirmed the predictive performance of the model. The observations outside the percentile range were randomly scattered, not aggregated at a particular time point. These findings indicated that the final model has adequate predictive performance to describe the measured sulbactam concentrations.
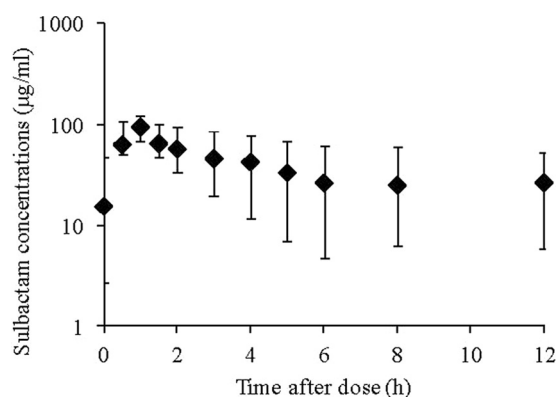
FIG 1 Plot between observed sulbactam concentrations in plasma (median ± interquartile range) versus time after the start of infusion on the 4th day of the treatment (a 1-h infusion of 2 g every 12 h of sulbactam).

TABLE 2 Population PK parameters of sulbactam in 27 patients with severe sepsis calculated from the final model[a]

Population PK parameter	Estimate	Interindividual variability (% CV)
V_c (liters)	14.56	52.0
V_p (liters)	9.55	53.1
CL (liters/h)		
Age > 65 yr	2.26	48.4
Age ≤ 65 yr	7.64	
Q (liters/h)	11.50	51.4

[a] V_c, central volume of distribution; V_p, peripheral volume of distribution; CL, total clearance; Q, intercompartmental clearance; % CV, percentage of coefficient of variation.

The PTAs for the different sulbactam regimens at specific MICs, with targets of 40% $T_{>MIC}$ and 60% $T_{>MIC}$, are shown in Table 4. The PTAs for different 4-h infusions of sulbactam at specific MICs, with targets of 40% $T_{>MIC}$ and 60% $T_{>MIC}$, are shown in Fig. 4. The PTAs for achieving 40% $T_{>MIC}$ and 60% $T_{>MIC}$ of the 4-h infusion regimens were greater than those for the 1-h infusion regimens. For pathogens with a MIC of 4 μg/ml, the PTAs of achieving 40% $T_{>MIC}$ following administration of a 4-h infusion of 1 g every 12 h, 1 g every 8 h, and 1 g every 6 h of
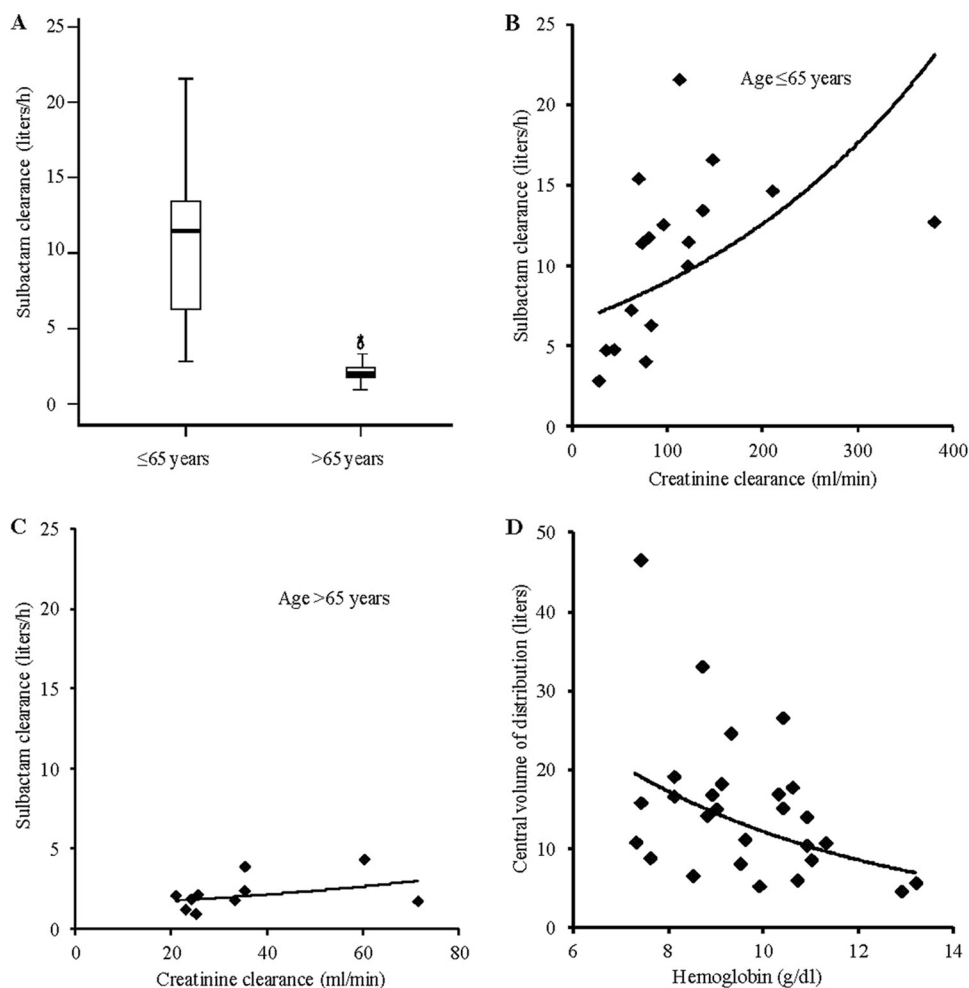

FIG 2 Plots between significant covariates and PK parameters. (A) Box plots of sulbactam clearance in patients aged ≤65 years and >65 years; (B) creatinine clearance versus sulbactam clearance of patients aged ≤65 years; (C) creatinine clearance versus sulbactam clearance of patients aged >65 years; (D) hemoglobin versus central volume of distribution.

TABLE 3 Parameter estimates of the base and final models[a]

Parameter	Base model[b] (MOFV = 1405.829)		Final model[c] (MOFV = 1350.030)		
	Estimate	% RSE	Estimate	% RSE	95% CI of bootstrap estimate
Fixed-effect parameters					
θ_1	1.66	10.7	0.54	17.5	−0.78 to 1.07
θ_5			0.28	3.9	−0.19 to 1.56
θ_6			1.57	6.0	0.82 to 2.12
θ_7			0.46	1.2	0.16 to 1.23
θ_2	2.58	4.5	4.56	2.3	2.85 to 5.61
θ_8			−1.88	0.9	−2.78 to −0.22
θ_3	2.78	5.4	2.26	5.4	2.08 to 2.93
θ_4	2.91	4.6	2.44	4.2	1.89 to 2.83
Interindividual variability (exponential model)					
IIV on CL (% CV)	92.8		48.4		
IIV on V_c (% CV)	59.1		52.0		
IIV on V_p (% CV)	72.3		53.1		
IIV on Q (% CV)	67.6		51.4		
Residual variability (combined additive and proportion model)					
Additive error (µg/ml)	2.24		2.52		
Proportional error (% CV)	7.5		7.6		

[a] % RSE, percentage of relative standard error; θ, population mean value; IIV, interindividual variability; % CV, percentage of coefficient of variation.

[b] Base model PK parameters: CL (liters/h), e^{θ_1}; V_c (liters), e^{θ_2}; V_p (liters), e^{θ_3}; Q (liters/h), e^{θ_4}. Abbreviations: MOFV, minimum objective function value; CL, total clearance; V_c, central volume of distribution; V_p, peripheral volume of distribution; Q, intercompartmental clearance; CL_{CR}, creatinine clearance.

[c] Final model PK parameters: CL (liters/h), $e^{\theta_1 + \theta_5 (CL_{CR}/30)}$ (for patients aged >65 years) and $e^{\theta_6 + \theta_7 (CL_{CR}/83)}$ (for patients aged ≤65 years); V_c (liters), $e^{\theta_2 + \theta_8 (Hgb/9.5)}$; V_p (liters), e^{θ_3}; Q (liters/h), e^{θ_4}. Abbreviation: Hgb, hemoglobin.

sulbactam were 92.54%, 99.55%, and 99.67%, respectively. For pathogens with a MIC of 8 µg/ml, the PTAs of achieving 40% $T_{>MIC}$ following administration of a 4-h infusion of 1 g every 8 h, 1 g every 6 h, and 2 g every 12 h of sulbactam were 94.30%, 96.65%, and 92.37%, respectively. For pathogens with a MIC of 4 µg/ml, the PTAs of achieving 60% $T_{>MIC}$ following administration of a 4-h infusion of 1 g every 12 h, 1 g every 8 h, and 1 g every 6 h of sulbactam were 77.12%, 92.56%, and 99.31%, respectively. For pathogens with a MIC of 8 µg/ml, the PTAs of achieving 60% $T_{>MIC}$ following administration of a 4-h infusion of 1 g every 8 h, 1 g every 6 h, and 2 g every 12 h of sulbactam were 81.65%, 93.37%, and 77.12%, respectively.

DISCUSSION

Although pathophysiological conditions are relatively stable in most patients, in critically ill patients with sepsis, changes in these conditions can occur, resulting in changes in V and CL for antimicrobial agents (17). An extravasation of a large volume of fluid into the interstitial space and tissue edema, associated with increased capillary leakage and the use of inotropes during the treatment of septic shock, can lead to a larger V than the values obtained from healthy subjects. Increased renal clearance resulting from increased cardiac output during the initial hyperdynamic state of severe sepsis and, on the other hand, decreased renal clearance with end-organ dysfunction can be observed with severe sepsis and septic shock (12, 17, 18). Our population PK studies of sulbactam were performed during the steady state on the 4th day of sulbactam administration, and the two-compartment model was the best model for describing the concentration-time profile of sulbactam, which was consistent with the results of previous population PK studies (11, 19, 20). The central V (V_c) and periph-

eral V (V_p) of sulbactam were 14.56 and 9.55 liters, respectively, which are greater than the values obtained from previous studies in patients with impaired renal function (11) and healthy volunteers (21). In addition, in the current population PK analysis, we found that the low hemoglobin value had a significant effect, resulting in an increased V_c of sulbactam. These findings may be explained by noting that the study was conducted on patients with seriously severe sepsis caused by MDR *A. baumannii*. Most recruited patients had an APACHE II score of ≥18 and a positive fluid balance from receiving a volume of fluid for the management of severe sepsis, resulting in a shift of fluid from the intravascular space into the interstitial space, which had the subsequent effect of increasing the V of sulbactam. Moreover, the protein binding of this agent is approximately 38%, and an earlier study clearly demonstrates that only the free fraction of the drug in serum or plasma correlates with antimicrobial efficacy (22). All enrolled patients had hypoalbuminemia, which may have been due to the decrease in protein synthesis from the liver, as well as increased capillary permeability and leakage into interstitial space in severe illness, leading to higher free-drug concentrations and tissue distribution. The CLs of sulbactam in the current study were 2.26 liters/h and 7.64 liters/h in patients aged >65 years and ≤65 years, respectively, which are lower than the values obtained from our previous study in healthy volunteers (21). Moreover, we found that the CL_{CR}s of most recruited patients decreased during the PK studies on the 4th day of antibiotic therapy compared to their initial CL_{CR}s at enrollment. A possible explanation for the decrease in the CL of sulbactam in this study is that this agent is eliminated mainly via glomerular filtration and tubular secretion and decreased renal perfusion occurs during life-threatening severe sepsis caused by
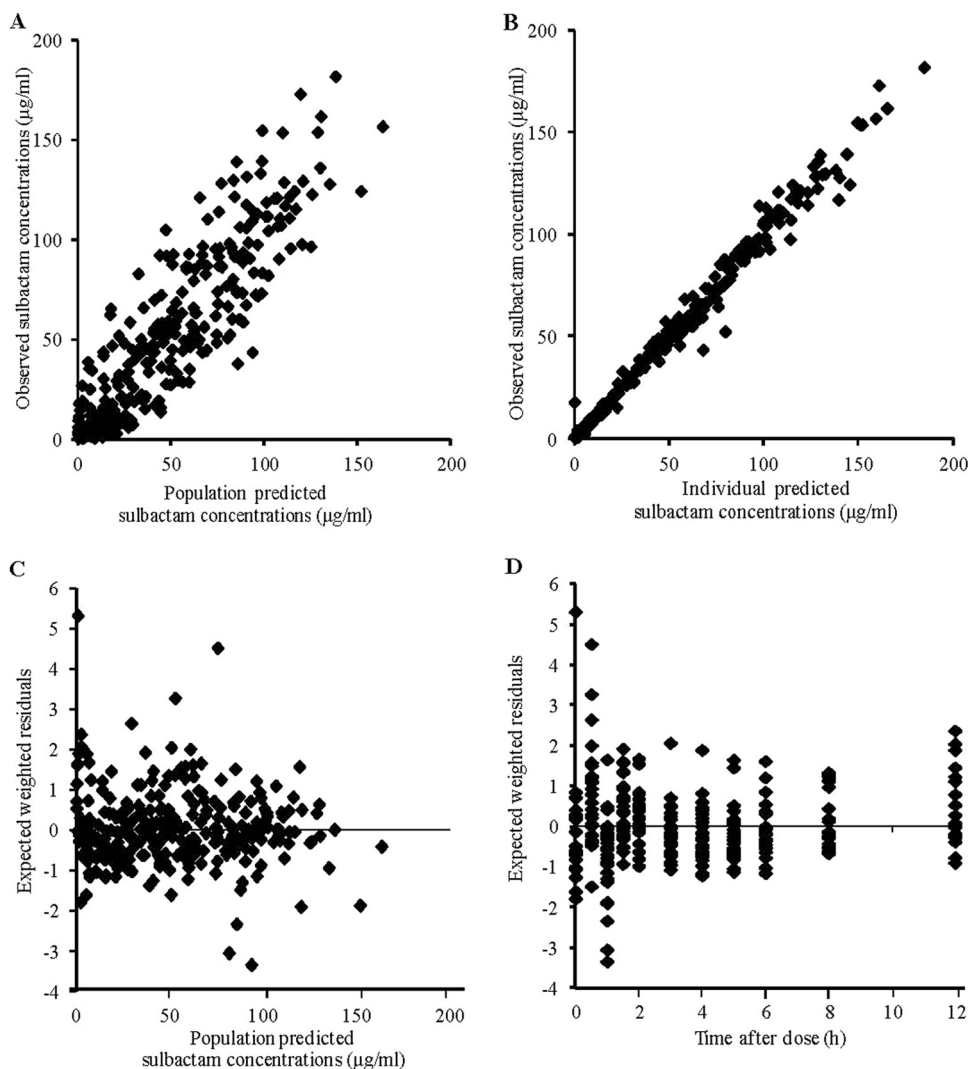
FIG 3 Diagnostic plots of the final model. (A) Observed sulbactam concentrations versus population predicted sulbactam concentrations; (B) observed sulbactam concentrations versus individual predicted sulbactam concentrations; (C) expected weighted residuals versus population predicted sulbactam concentrations; (D) expected weighted residuals versus time after dose.

MDR *A. baumannii*, leading to the impairment of renal function. In addition, all patients were receiving several concomitant medications, particularly colistin, which is known to cause renal dysfunction in some patients. However, from the population PK analysis in this study, we found that the decrease in CL of sulbactam was significantly correlated with only the decreased CL_{CR} of patients aged ≤65 years, not that of patients aged >65 years. The evaluation of renal function by estimated CL_{CR} (determined by the Cockcroft-Gault method) for predicting the CL of sulbactam may not be the best method in geriatric patients. In conclusion, the PK changes of sulbactam in the present study had an effect on the plasma concentrations, and dosage adjustment should be considered in this patient population to achieve therapeutic concentrations.

Studies in animal infection models have shown that for most β-lactams, drug concentrations do not need to exceed the MIC for 100% of the dosing interval in order to achieve a significant antibacterial effect (23, 24). A previous PK/PD analysis of sulbactam in *in vitro* and murine thigh and lung infection models found that bacteriostatic effects of sulbactam against *A. baumannii* in murine thigh and lung infections model were observed when the $fT_{>MIC}$ targets were approximately 20%, whereas the $fT_{>MIC}$ targets required for bactericidal activity in murine thigh and lung infection models were 40% and 30%, respectively. However, for severe infections in immunocompromised hosts, the $fT_{>MIC}$ targets required for sufficient bactericidal effects against *A. baumannii* thigh and lung infections were increased to >60% and >40%, respectively (25). A previous population PK/PD target attainment analysis to optimize dosage regimens of sulbactam in patients with renal dysfunction found that a regimen of 1 g twice daily could achieve the PK/PD target attainments with a MIC of 2 μg/ml and a regimen of 2 g four times daily could achieve those with a MIC of 16 μg/ml (11). Moreover, other previous studies in critically ill patients with VAP also found that a high-dosage regimen of an ampicillin-sulbactam combination was effective and safe as an alternative treatment option for MDR *A. baumannii* infections

TABLE 4 Probability of target attainment (PTA) for sulbactam regimens achieving 40% $T_{>MIC}$ and 60% $T_{>MIC}$ in 27 patients with severe sepsis caused by *A. baumannii*[a]

Dosage regimen	Duration of infusion (h)	MIC (μg/ml)	Probability of attaining a %$T_{>MIC}$ of:	
			40%	60%
1 g q12h	1	1	93.38	84.88
		2	89.55	78.62
		4	82.81	69.18
	4	1	98.81	91.46
		2	97.11	86.21
		4	92.54	77.12
1 g q8h	1	2	95.80	89.43
		4	91.94	82.79
		8	83.55	71.46
	4	2	99.97	97.05
		4	99.55	92.56
		8	94.30	81.65
		16	71.21	59.49
1 g q6h	1	4	95.85	89.81
		8	90.38	81.21
		16	76.66	65.29
	4	4	99.67	99.31
		8	96.65	93.37
		16	81.19	74.66
2 g q12h	1	1	95.86	89.02
		2	93.42	84.79
		4	89.48	78.53
		8	82.73	69.09
	4	1	99.49	94.51
		2	98.78	91.30
		4	97.04	86.13
		8	92.37	77.12
2 g q8h	1	8	91.81	82.76
		16	83.47	71.55
		32	65.66	52.86
	4	8	99.56	92.55
		16	94.28	81.62
		32	71.14	59.52
2 g q6h	1	8	95.94	89.96
		16	90.50	81.35
		32	76.76	65.46
	4	8	99.68	99.36
		16	96.73	93.43
		32	81.30	74.85
3 g q8h	1	4	97.07	92.07
		8	94.57	87.25
		16	89.35	78.94
		32	77.75	64.96
	4	8	99.92	95.73
		16	98.61	89.22
		32	87.37	73.94
3 g q6h	1	16	94.21	86.97
		32	86.18	75.89
		64	67.05	56.11
	4	16	99.09	98.02
		32	92.56	87.53
		64	69.41	63.15

TABLE 4 (Continued)

Dosage regimen	Duration of infusion (h)	MIC (μg/ml)	Probability of attaining a %$T_{>MIC}$ of:	
			40%	60%
4 g q8h	1	8	95.80	89.43
		16	91.93	82.83
		32	83.59	71.51
	4	16	99.55	92.60
		32	94.31	81.71
		64	71.25	59.46
3 g q24h	24	8	88.17	88.17
6 g q24h	24	8	97.47	97.47
9 g q24h	24	16	94.92	94.92
12 g q24h	24	32	88.05	88.05

[a] q12h, every 12 h; %$T_{>MIC}$, percentage of the dosing interval during which drug concentration in tissue and serum were above the MIC.

(26, 27). In the current study, we examined the population PK of sulbactam for the treatment of patients with severe sepsis caused by MDR *A. baumannii* and performed a Monte Carlo dosing simulation to determine the probability of attaining specific PD targets using various regimens. The results of our study are similar to the results from previous studies with β-lactam antimicrobial agents (28, 29), in finding that the PTAs for achieving 40% $T_{>MIC}$ and 60% $T_{>MIC}$ of the 4-h prolonged infusion regimens of sulbactam were greater than those of the 1-h infusion regimens. Therefore, a prolonged infusion time was a more effective strategy to achieve optimal PD exposure for pathogens with higher MICs than dose escalation. The high PTAs (≥90%) achieving 40% $T_{>MIC}$ for a MIC of 4 μg/ml were observed when sulbactam was administered by a 4-h infusion of 1 g every 12 h. For pathogens with a MIC of 8 μg/ml, the high PTAs were achieved when the dosages of sulbactam were increased to a 4-h infusion of 1 g every 8 h, 1 g every 6 h, and 2 g every 12 h. For pathogens with a MIC of 16 μg/ml, the high PTAs were achieved when the dosages of sulbactam were increased to a 4-h infusion of 2 g every 8 h, 2 g every 6 h, and 3 g every 8 h; and a 4-h infusion of 3 g every 6 h and 4 g every 8 h achieved the high PTA of 40% $T_{>MIC}$ for a MIC of 32 μg/ml. These data indicate that 1 g of sulbactam every 12 h can provide good coverage for pathogens with MICs of ≤4 μg/ml; for less-susceptible pathogens with MICs of >4 μg/ml, the dosage regimens should be increased in order to achieve optimal antimicrobial activity. However, the continuous infusion of sulbactam did not achieve higher PTAs than the prolonged infusion of sulbactam at the same total daily dose.

The current study also examined the probabilities of dosage regimens of sulbactam achieving targets of 60% $T_{>MIC}$ for the treatment of life-threatening infections in immunocompromised hosts and found that the high PTAs for MICs of 4 μg/ml, 8 μg/ml, and 16 μg/ml were obtained when sulbactam was administered by a 4-h infusion of 1 g every 8 h, 1 g every 6 h, and 2 g every 6 h, respectively. In addition, for pathogens with a MIC of 32 μg/ml, the high PTAs were achieved when sulbactam was administered by a continuous infusion of 12 g every 24 h. Therefore, the results from the current study indicate that in immunocompromised hosts with severe sepsis, 1 g of sulbactam every 8 h can provide good coverage for patients infected with pathogens with MICs of
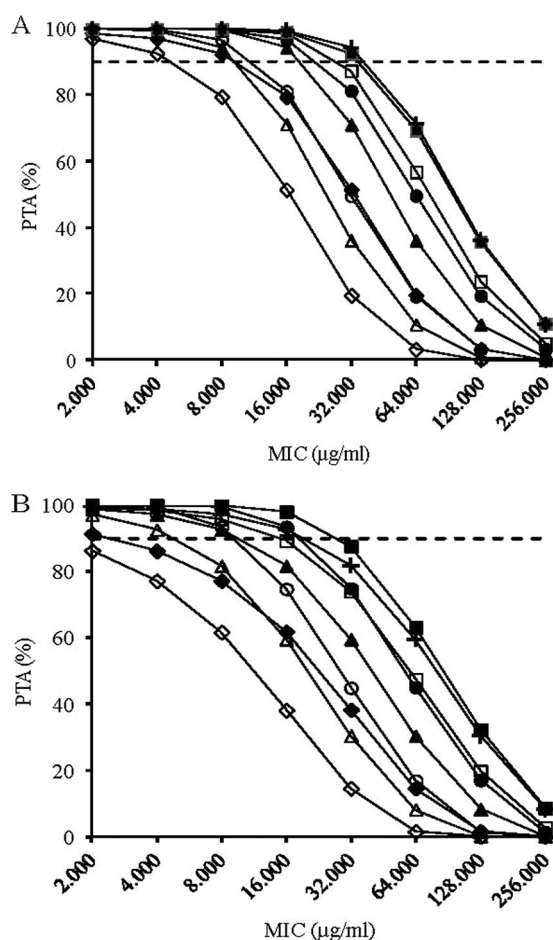
FIG 4 Probability of target attainment (PTA) for sulbactam regimens achieving 40% $T_{>MIC}$ (A) and 60% $T_{>MIC}$ (B) at specific MICs in 27 patients with severe sepsis caused by *A. baumannii* after administration of sulbactam in a 4-h infusion of 1 g every 12 h (◇), a 4-h infusion of 1 g every 8 h (△), a 4-h infusion of 1 g every 6 h (○), a 4-h infusion of 2 g every 12 h (◆), a 4-h infusion of 2 g every 8 h (▲), a 4-h infusion of 2 g every 6 h (●), a 4-h infusion of 3 g every 8 h (□), a 4-h infusion of 3 g every 6 h (■), and a 4-h infusion of 4 g every 8 h (✚). The broken line represents 90% PTA. $T_{>MIC}$, time that concentrations in tissue and serum are above the MIC.

≤4 µg/ml, and for less-susceptible pathogens with a MIC of 32 µg/ml, a higher dosage of 12 g every 24 h of sulbactam, administered by continuous infusion, may be required. However, a higher-dosage regimen should be used with caution because of the risk of toxicity, even though it appears that the standard dosage regimen of sulbactam is well tolerated with few adverse events.

The MIC_{50} and MIC_{90} of sulbactam against isolated *A. baumannii* from the current study were comparable to the MIC distributions of sulbactam for *A. baumannii* from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database but higher than the findings from a previous study in Japan (11). The combination of sulbactam with the other effective antimicrobial agent for *A. baumannii*, colistin, was prescribed in all patients for the treatment of infections in our study. Most *A. baumannii* infections in these patients were eradicated after 10 days of treatment, except for four *A. baumannii* infections in patients with VAP. Among the four patients with persistent *A. baumannii* infections, three were infected with *A. baumannii* isolates

with MICs of 48 µg/ml and one was infected with an *A. baumannii* isolate with a MIC of 8 µg/ml. However, the efficacy of sulbactam for the treatment against *A. baumannii* infections could not be fully evaluated because the patients were also receiving concomitant therapy with colistin and other β-lactam antibiotics. During the sulbactam administration in the current study, no major adverse events related to this agent were observed.

The current study had a few limitations that must be considered. First, the plasma concentrations of sulbactam in this study were total drug concentrations, whereas only free-drug concentrations were used for calculating the PK/PD index to determine the antimicrobial activity of this agent. And second, the study was performed with low-body-weight patients, which might have had an effect on *V* and CL, and therefore the results of this study may be difficult to extrapolate to other situations.

In conclusion, the current study of population PK in critically ill patients with severe sepsis caused by MDR *A. baumannii* found that the *V* of sulbactam was greater than, and the CL of sulbactam was lesser than, the values obtained from a previous study with healthy subjects. The high PTAs (≥90%) for targets of 40% $T_{>MIC}$ and 60% $T_{>MIC}$ with a MIC of 4 µg/ml were observed when sulbactam was administered by a 4-h infusion of 1 g every 12 h and 1 g every 8 h, respectively. These findings indicate that these dosage regimens of sulbactam may be an alternative antibiotic option for coadministration with colistin, a commonly prescribed antimicrobial agent, for the treatment of infections caused by MDR *A. baumannii*. However, against less-susceptible pathogens with MICs of >4 µg/ml, higher-dosage regimens of sulbactam are required to achieve the PD targets for effective antimicrobial therapy.

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